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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
CHUNDURU, SURYAPRABHA	
ART UNIT	**PAPER NUMBER**
1637	

DATE MAILED: 04/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/839,649	MURCHIE ET AL.	
	Examiner	Art Unit	
	Suryaprabha Chunduru	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 January 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13 and 16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicants' response to the office action filed on January 5, 2004 has been entered.

2. Claims 1-13 and 16 are pending.

3. This application is filed on April 19, 2001 and claims benefit of a US provisional application 60/198,179 filed on April 19, 2000.

Response to Arguments

4. Applicants' response to the office action is fully considered and found not persuasive.

5. With regard to the rejection made in the previous office action under 35 USC 112, second paragraph, Applicants' arguments are fully considered and found not persuasive. Applicants' argue that the instant specification provides clear definition for the term " suicide substrate" in claim 16, and hence the rejection be withdrawn. This argument is fully considered, however, As stated in the MPEP 2145, "Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims". In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993), the instant claims do not recite structural limitation and specification is not be read into the claims. Therefore the rejection is maintained herein.

6. The following is the rejection made in the previous office action under 35 USC 102(b):

A. Claim 1-11 are rejected under 35 U.S.C. 102(b) as being anticipated by Hansen et al. (RNA, Vol.5, pp. 93-101, 1999).

With reference to the instant claim 1, Hansen et al. teach a method for determining whether a test compound (DMA or kethoxal) binds to a target RNA, wherein Hansen et al. discloses that the method comprises (a) contacting said test compound with said target RNA and

an RNA-modifying enzyme (ErmE methyltransferase) (see page 100, column 1, paragraphs 2-4) that covalently alters an existing base in said target RNA (see page 98, column 1, paragraph 1, Fig.3); (b) detecting the modification of said target RNA by said enzyme and comparing the amount of modification to that of a standard (untreated control), wherein said comparison determines whether said test compound binds to said target RNA (see page 100, column 1, paragraph 4, page 97, Fig.2, page 96, column 1, Fig.1).

With reference to claims 2-11, Hansen et al. also disclose that the method comprises ribosomal RNA target (see page 100, paragraph 2); (ii) target RNA includes a stabilizing structure and chemical modification enhances the stability of said target RNA (see page 98, column 1, paragraph 1); (iii) RNA modifying enzyme is erythromycin resistance (ErmE) methyltransferase (see page 100, column 1, paragraphs 1-2); (iv) target RNA modification is detected by incorporation of a radio label S-adenosyl-methionine into the target RNA (see page 100, column 1, paragraph 2, page 95, table.1); and (v) the test compound is a small organic molecule (DMS or kethoxal) (see page 100, column 1, paragraph 3). Thus the disclosure of Hansen et al. meets the limitations in the instant claims.

Response to arguments :

With regard to the above rejection, applicants' arguments are fully considered and found not persuasive. Applicants argue that Hansen et al. reference fail to teach every element of the instant claim 1 and Hansen et al teach methylation of target 23S ribosomal RNA by ErmE methyltransferases in the presence of magnesium concentration. Applicants also argue that the test compounds (DMS and kethoxal) taught by Hansen et al. was carried out in a separate experiment with out the presence of the enzyme (ErmE methyltrnasferases) and does not teach

the binding of a test compound to the target RNA rather teach probing the secondary structure of 23S rRNA by the test compounds. Applicants' arguments are fully considered and found not persuasive fro two reasons first, the instant claim 1 recites "detecting the modification of said target RNA by said enzyme and comparing said modification....", and thus modification includes modified methylation motifs or domains on the said target RNA, second, Hansen et al. teach treating the bacterial strains with test compound (tetracycline) (see page 372, column 2, 2nd paragraph under the heading materials and methods), and detecting the modification (methylation) and detecting the modification of the target in the presence of ErmE in the same reaction vessel (see page 373, column 1, paragraph 2, under sub title analysis of methylation), indicating that the detection of modification of said target RNA was done in the presence of a test compound and the ErmE enzyme. Further, the instant claim 1 is in 'comprising' format and thus any additional steps are permitted, and also does not exclude reactions carried out in separate vessels. Moreover, the limitation " one vial" is not present in the instant claim. Therefore the rejection is maintained.

6. The following is the rejection made in the previous office action under 35 USC 102(e):

B. Claims 1-7, 9, 11 rejected under 35 U.S.C. 102(e) as being anticipated by Schwartz et al. (USPN. 6,020,139).

Schwartz et al. teach a method for determining whether a test compound binds to a target nucleic acid, wherein Schwartz et al. disclose that the method comprises (a) contacting said test compound with the target sample (biological fluid comprising nucleic acids) comprising RNA-modifying enzyme (S-adenosylhomocystenine hydrolase, or methyl transferases) which form s-adenosyl-L-methionine (SAM) metabolite (see column 15, lines 16-65, column 16, lines 31-41)

that covalently alters an existing base in the target sample (see column 15, lines 33-65, column 5, lines 64-67, column 6, lines 1-27, column 11, lines 62-67, column 12, lines 1-57); (b) detecting the modification of said target nucleic acid by said enzyme and comparing the amount of modification detected to that of a standard and identifying the binding of said test compound with said target RNA (see column 6, lines 3-40, column 5, lines 26-46). Schwartz et al. also teach that the (i) RNA target comprises ribosomal RNA (see column 14, lines 50-57); target RNA includes stabilizing methylated (chemical modification) structure (see column 32, lines 11-50); RNA-modifying enzyme comprises methyltransferase (column 15, lines 32-44); RNA modification is detected by the incorporation of radiolabeled SAM (see column 5, lines 26-46); test compound is selected from the group consisting of peptide, protein, lipid, small molecule, nucleotides and a polyamine (see column 7, lines 1-61). Thus the disclosure of Schwartz et al. meets the limitations in the instant claims.

Response to the arguments:

With regard to the above rejection applicants' arguments are fully considered and found not persuasive. Applicants argue that Schwarts et al. fail to teach "the binding of said test compound with said target RNA" and does not teach inhibition of SAM-mediated methylation by test compound via binding to the target. The arguments are fully considered and found not persuasive because the modification of said target RNA is a result of the effect of a test compound on the said target, which indicates that the test compound binds to the target and results in altering the target RNA, without binding of a test compound to the target, it would not result in a modified target. Thus 'binding' is an inherent property, whose effect is clearly seen as a result, which in the instant case, a modified target. Applicants' arguments on the property of inherency is fully

considered, however, the instant claim does not exclude the binding of the test compound to the enzyme and then to the target RNA, because the instant claim recites contacting a test compound with said target RNA and an RNA-modifying-enzyme that covalently alters an existing base in said target RNA. Thus the inherency flows from the prior art reference and therefore the rejection is maintained herein.

7. The following is the rejection made in the previous office action under 35 USC 102(b):

Claim 1-4, 16 is rejected under 35 U.S.C. 102(b) as being anticipated by Glazer et al. (J Biol. Chem., Vol. 259, No.21, pp. 12964-12969, 1984).

Glazer et al. teach a method for determining a test compound (neplanocin A) binds to a target RNA, wherein Glazer et al. teach that the method comprises (a) contacting a test compound with a RNA-modifying enzyme (RNA methyltransferase) and said target RNA comprising suicide substrate (cytocidal substrate) for said enzyme (see page 12964, column 1, summary, column 2, paragraphs 1-8); (b) detecting the modification of the enzyme by said suicide substrate (decreased RNA methylation), wherein said detecting determines whether said test compound binds to said target RNA (see page 12965, column 1, paragraphs 1-5, column 2, paragraph 1-2). Thus the disclosure of Galzer et al. meets the limitations in the instant claim.

Response to arguments:

With regard to the above rejection applicants' arguments are fully considered and found not persuasive. Applicants argue that NPC binds to the enzyme and then result in modification of the target and does not teach binding of the test compound to the target. As discussed above, the claim 1 does not exclude the binding of the test compound to the enzyme and then to the target RNA, because the instant claim recites contacting a test compound with said target RNA and an

RNA-modifying-enzyme that covalently alters an existing base in said target RNA. Thus the inherency flows from the prior art reference and therefore the rejection is maintained herein.

8. The following is the rejection made in the previous office action under 35 USC 103(a):

Claims 12-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hansen et al. (RNA, Vol.5, pp. 93-101, 1999) in view of Karn et al. (USPN. 6,316,194).

Hansen et al. teach a method for determining whether a test compound (DMA or kethoxal) binds to a target RNA, wherein Hansen et al. discloses that the method comprises (a) contacting said test compound with said target RNA and an RNA-modifying enzyme (ErmE methyltranferase) (see page 100, column 1, paragraphs 2-4) that covalently alters an existing base in said target RNA (see page 98, column 1, paragraph 1, Fig.3); (b) detecting the modification of said target RNA by said enzyme and comparing the amount of modification to that of a standard (untreated control), wherein said comparison determines whether said test compound binds to said target RNA (see page 100, column 1, paragraph 4, page 97, Fig.2, page 96, column 1, Fig.1). Hansen et al. also disclose that the method comprises ribosomal RNA target (see page 100, paragraph 2); (ii) target RNA includes a stabilizing structure and chemical modification enhances the stability of said target RNA (see page 98, column 1, paragraph 1); (iii) RNA modifying enzyme is erythromycin resistance (ErmE) methyltransferase (see page 100, column 1, paragraphs 1-2); (iv) target RNA modification is detected by incorporation of a radio label S-adenosyl-methionine into the target RNA (see page 100, column 1, paragraph 2, page 95, table.1); and (v) the test compound is a small organic molecule (DMS or kethoxal) (see page 100, column 1, paragraph 3). However, Hansen et al. did not teach test compound selected from combinatorial library and high throughput assay format.

Karn et al. teach a method for determining a test compound binds to a target RNA, wherein Karn et al. disclose that the method comprises (i) incubating a test compound with target RNA and an antimicrobial molecule, measuring or detecting the change or modification of said target RNA and comparing the amount of change to that of a standard and identifying test compounds that bind to the target RNA (see column 3, lines 51-67, column 4, lines 1-26). Karn et al. also disclose that the method comprises (i) target RNA as ribosomal RNA or fragment or sub-regions of ribosome or complete RNA (see column 4, lines 36-42, column 5, lines 53-67, and column 6, lines 1-7); (ii) target RNA could be chemically modified RNA which enhances the stability of said target RNA (see column 4, lines 36-38, column 9, lines 2-66, column 10, lines 4-67); test compounds could include peptides, peptides, lipids, metal, nucleotides, nucleosides, small organic molecules, polyamines (see column 15, lines 62-67, and column 16, lines 1-11); test compounds may be derived from large libraries of synthetic or natural compounds (combinatorial library) (see column 16, lines 12-20); and the method is designed for a high-throughput screening format (see column 19, lines 30-46).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the method of detecting a test compound as taught by by Hansen et al. with the method of Karn et al. which is well known in the art at the time the invention was made, because Karn et al. states that 'In most biological systems, the functions of RNA is often determined by the interactions between highly conserved RNA structures. In many instances it is desirable to develop drugs that bind RNA at sites of conserved structure to act as competitive inhibitors of the RNA function that is derived from various RNA interactions. These types of drugs have potential applications in a wide range of diseases including bacterial, viral,

and fungal infections. Many antibiotics function by inhibiting protein synthesis, and it has become increasingly clear that many do so by acting at the level of ribosomal RNA" (see column 1, lines 13-21 and column 2, lines 61-63). An ordinary practitioner would have been motivated to combine the method of Hansen et al. with the addition of high-throughput assay format and use of combinatorial library as taught by Karn et al. because the addition of such limitations would improve the method for simultaneous screening of different test compounds binding to target ribosomal RNA.

Response to arguments:

With regard to the above rejection, applicants' arguments are fully considered and found not persuasive. Applicants' argue that there is no teaching or suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir.1992). In this case, specific motivation is provided by the teachings of Hansen et al. in view of Karn et al. This is not a case of a rubber polymer to discuss the merits of establishing obviousness. In the instant case an ordinary practitioner would have been motivated to combine the method of Hansen et al. with the addition of high-throughput assay format and use of combinatorial library as taught by Karn et al. because the addition of such limitations would improve the method for simultaneous screening of different test compounds binding to target ribosomal RNA. Therefore the rejection is maintained herein.

Conclusion

No claims are allowable.

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Suryaprabha Chunduru whose telephone number is 571-272-0783. The examiner can normally be reached on 8.30A.M. - 4.30P.M, Mon - Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and - for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Suryaprabha Chunduru
March 31, 2004

JEFFREY FREDMAN
PRIMARY EXAMINER